On the path to eliminating malaria

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Malaria kills more than 400,000 people each year, many of them children in Sub-Saharan Africa. Australian scientist David Fidock from Columbia University has uncovered the genetic basis for drug resistance in deadly malaria parasites, and is now working on new drugs that will aid the global effort to eradicate malaria once and for all.

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Chloroquine was used to fight malaria shortly after World War Two, becoming one of the most successful drugs ever deployed against an infectious disease.

“It was the household Tylenol,” says Professor David Fidock, a molecular biologist and geneticist at Columbia University in New York. “It was present throughout all malaria-endemic areas. Any initial symptoms of fever and that’s what you took, because it was presumed to be malaria.”

At its peak use, there were an estimated 300 million doses taken per year. This heavy usage saw the most deadly malaria parasite, Plasmodium falciparum, develop a resistance to chloroquine.

In areas where malaria had nearly been eradicated, it re-emerged with deadly force. For decades, exactly how the parasite had acquired this resistance remained a mystery.

> This changed in 1999 thanks to Fidock. The Australian scientist was working at the National Institutes of Health (NIH) in Washington, in the lab of malaria researcher Thomas Wellems, who had evidence that a single mutant gene was to blame for the resistance.

It was Fidock who correctly identified that gene, called PfCRT, which they described in the journal Molecular Cell. The discovery changed the course of malaria research and treatment strategies globally, enabling a simple molecular test to diagnose the extent of resistance.

Changing the course of malaria research

With resistance verified around the world, the once overused chloroquine was replaced with more effective antimalarial drugs.

In the years since, the global research community has made significant progress battling malaria. Mortality rates dropped by 60 per cent between 2000 and 2015, resulting in an estimated 6.2 million averted deaths, according to the World Health Organization.

But the toll is still frighteningly high: more than 400,000 people are killed each year, says Fidock, and greater than 80 per cent are children below the age of five in Sub-Saharan Africa.

In the last few years, malaria parasites have also begun developing resistance to another frontline drug known as artemisinin. It was Fidock who, in 2015, provided definitive genetic evidence that mutations in the K13 gene drive this resistance.

As with chloroquine, this discovery provides a molecular signature to identify where resistance has occurred, and to alter treatment strategies accordingly, he says.

Fidock was recently honoured at the 2016 Advance Global Australians Awards, winning in the Life Sciences category for his significant contributions to malaria research. His overarching mission, Fidock says, is to help eradicate malaria globally, or at least “shrink the map” of affected areas.

Doing so means trying to constantly outsmart these highly complex, ever-evolving parasites.

Professor David Fidock at the Advance Global Australians awards. Credit: Advance Global Australians.

Seeing the disease in the flesh

Born at a NATO base in France, Fidock moved to Australia with his family at age seven. He completed a Bachelor of Mathematical Science at the University of Adelaide, where he focused on genetics.

Compelled to address global health issues largely ignored by big pharmaceutical companies, Fidock returned to France in 1989 to undertake a PhD at the Institut Pasteur in Paris, where his work centred on malaria vaccines.

It was a year later while on a research trip to western Kenya that he first witnessed the horrific impact of the disease. “You could see kids coming in who were already in a coma, and you knew that most of them wouldn’t make it to the next day,” Fidock told the Columbia Medicine magazine. “It was shocking and humbling to understand that for these people, malaria was still an ever present part of life.”

After nine years, Fidock abandoned his search for a vaccine. He says it seemed unlikely to bear fruit, given the complex biology of the malaria parasite, which is able to change forms inside the body and enter different life stages as it moves from the liver to the bloodstream to evade detection.

> Fidock thought he could make a bigger impact by applying his expertise in genetics to understand how drug resistance was evolving. As it turns out, he was right.

The Fidock lab and testing new drugs

The breakthrough discovery of the PfCRT gene catapulted Fidock to a faculty position at the Albert Einstein College of Medicine in New York, and later Columbia University.

Now a Professor of Microbiology and Immunology, his lab of 16 researchers has published 160 papers and receives roughly US$1.5 million annually from the NIH, the US Department of Defense, the Bill and Melinda Gates Foundation, the Burroughs Wellcome Fund, and the Medicines for Malaria Venture in Geneva.

> The lab has helped pioneer the field of genome editing in malaria parasites, making it possible to quickly understand how resistance evolves and how specific drugs attack these organisms on a cellular and molecular level. The lab has also shown that some genetic mutations result in resistance to one drug, but make the parasite more susceptible to another.

If they can “lock parasites in these evolutionary dead ends”, they can eradicate them with combinations of drugs, Fidock says.

His lab also exposes parasites to drugs in the development pipeline, to assess how likely it is that a genetic resistance will evolve in the future – and how quickly.

Professor David Fidock with his award from Advance Global Australians. Credit: Advance Global Australians.

The Holy Grail of malaria research

Most antimalarial drugs target parasites that have invaded red blood cells, which is when the disease turns deadly. But Fidock wants to develop a new class of drug, like a malaria vaccine, which can detect the parasites at an even earlier stage when they are not yet detectable in the liver – their first port of call in a human host.

Inside liver cells, a form of the parasite rapidly produces up to 30,000 replicas over a seven-day period. It's these offspring that will go on to invade red blood cells and become transmissible. To reproduce on this scale, however, the parasites need energy scavenged from massive amounts of fatty acids.

Fidock hopes to genetically engineer parasites that are less adept at gathering these fatty acids and load them into a vaccine. The modified parasites would get stuck inside the liver for longer periods, generating a more robust immune response from the host.

> "That's the ultimate goal," says Fidock, "to find a drug that not only cures the infection, but eliminates all forms of the parasite in the body. We want to stop it from progressing to the disease-causing stage."

- Read more about David Fidock's work at Columbia University in New York.